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(54) Title: AMIDE COMPOUNDS FOR THE POTENTIATION OF CHOLINERGIC ACTIVITY		
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> $\begin{array}{c} R^1 \\ \diagdown \\ X-Y-Q-R^3 \\ \diagup \\ R^2 \end{array} \quad (I)$ </div> <div style="text-align: center;"> $\begin{array}{c} O \\ \\ -C- \end{array} \quad (1)$ </div> </div>		
(57) Abstract <p>Amide compounds of formula (I) wherein R¹ and R² are each aryl or ar(lower)alkyl, or are taken together to form lower alkylene or lower alkenylene, each of which may be substituted with aryl or may be condensed with a cyclic hydrocarbon optionally substituted with lower alkyl, lower alkoxy, aryl, aryloxy or halogen, R³ is lower alkyl, lower alkoxy, aryl, arylamino or aryloxy, each of which may be substituted with lower alkoxy or halogen, pyridyl, or pyridylamino, X is CH or N, Y is a single bond or -NH-, and Q is formula (1), and salt thereof, which are useful as medicament.</p>		

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DESCRIPTION

AMIDE COMPOUNDS FOR THE POTENTIATION OF CHOLINERGIC ACTIVITY

5 TECHNICAL FIELD

This invention relates to amide compounds and salts thereof which are useful as a medicament.

BACKGROUND ART

10 Some aminopiperazine derivatives have been known as useful anti-amnesia or anti-dementia agents, for example, in PCT International Publication Nos. WO 91/01979 and WO 98/35951.

15 DISCLOSURE OF INVENTION

This invention relates to amide compounds and salts thereof.

More particularly, it relates to amide compounds and salts thereof which have the potentiation of the cholinergic activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the treatment and/or prevention of disorders in the central nervous system for mammals, and more particularly to method for the treatment and/or prevention of amnesia, dementia (e.g. senile dementia, Alzheimer's dementia, dementia associated with various diseases such as cerebral vascular dementia, cerebral post-traumatic dementia, dementia due to brain tumor, dementia due to chronic subdural hematoma, dementia due to normal pressure hydrocephalus, post-meningitis dementia, Parkinson's disease type dementia, etc.), and the like. Additionally, the object compound is expected to be useful as therapeutical and/or preventive agents for schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy,

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attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

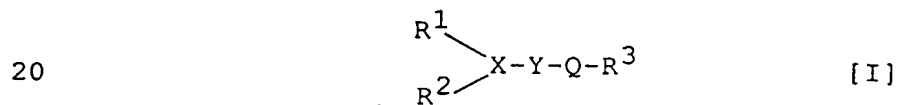
One object of this invention is to provide new and useful amide compounds and salts thereof which possess the
5 potentiation of the cholinergic activity.

Another object of this invention is to provide processes for preparation of the amide compounds and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active
10 ingredient, said amide compounds and salt thereof.

Still further object of this invention is to provide a therapeutic method for the treatment and/or prevention of aforesaid diseases in mammals, using the amide compounds and salts thereof.

The amide compounds of this invention can be represented by the following general formula [I]:



wherein R¹ and R² are each aryl or ar(lower)alkyl, or are taken together to form lower alkylene or lower alkenylene, each of which may be substituted with aryl or may be condensed with a cyclic hydrocarbon optionally substituted with lower alkyl, lower alkoxy, aryl, aryloxy or halogen, R³ is lower alkyl, lower alkoxy, aryl, arylamino or aryloxy, each of which may be substituted with lower alkoxy or halogen, pyridyl, or pyridylamino,

X is CH or N.

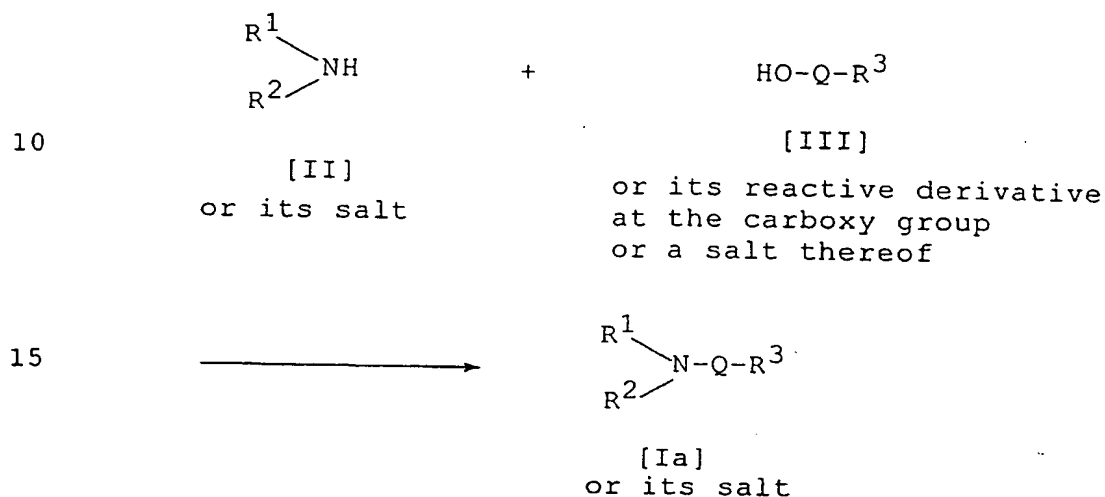
Y is a single bond or -NH-, and

35 Q is $\text{C}=\text{O}$,

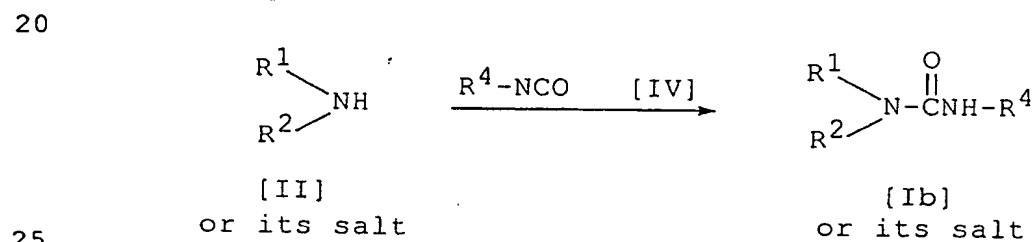
and salts thereof.

The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

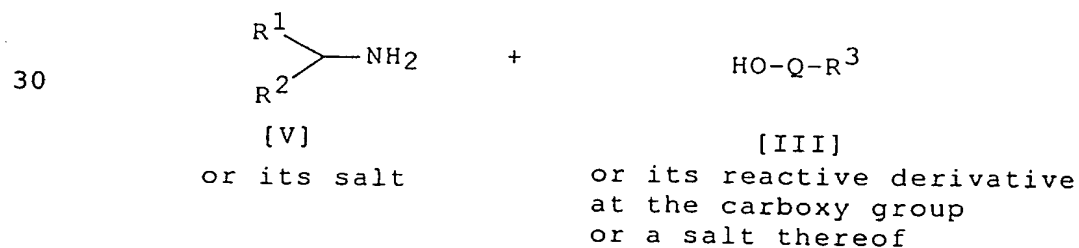
Process 1



Process 2



Process 3



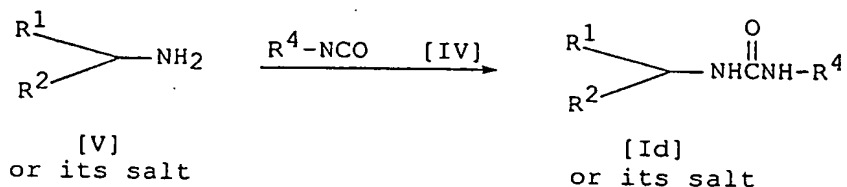
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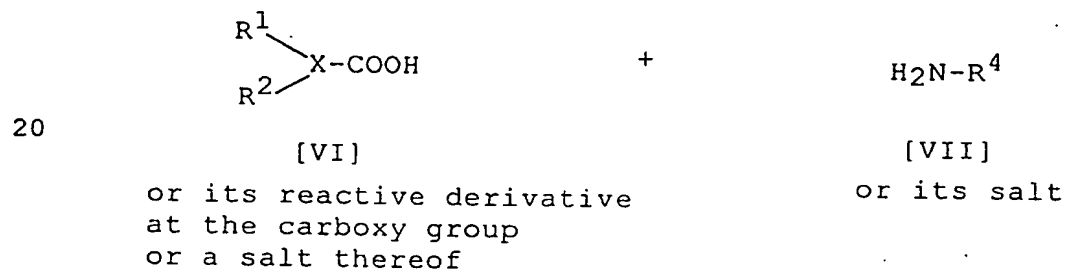
[Ic]
or its salt

Process 4

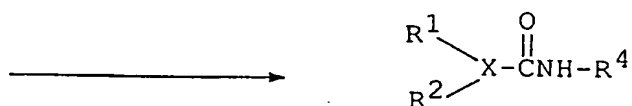
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Process 5

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[Ie]
or its salt

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wherein R^1 , R^2 , R^3 , X and Q are each as defined above, and
 R^4 is aryl which may be substituted with lower
 alkoxy or halogen, or pyridyl.

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In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

5

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety in the term "ar(lower)alkyl" may be a straight or branched C₁-C₆ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, ethylpropyl, hexyl or the like, in which preferable one is methyl.

Suitable "aryl" and aryl or ar moiety in the terms "ar(lower)alkyl", "aryloxy" and "arylamino" may be phenyl, naphthyl, pentyl substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, di(tert-butyl)phenyl, etc.] and the like, in which preferable one is phenyl.

Suitable "halogen" may be fluorine, chlorine, bromine and iodine, in which preferable one is fluorine.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, phenylpropyl, benzhydryl, trityl and the like, in which preferable one is benzyl.

Suitable "lower alkylene" may be a straight or branched C₁-C₆ alkylene such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, methylpentamethylene or the like, in which preferable one is tetramethylene or pentamethylene.

Suitable "lower alkenylene" may be a straight or branched C₂-C₆ alkenylene such as vinylene, propenylene, butenylene, pentenylene, methylpentenylene, hexenylene, pentadienylene or the like, in which preferable one is butenylene, pentenylene or methylpentenylene.

Suitable "lower alkoxy" may be a straight or branched

C₁-C₆ alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, methylpropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which preferable one is methoxy.

5 Suitable "cyclic hydrocarbon" may be a saturated or unsaturated cyclic hydrocarbon such as cyclopentane, cyclohexane, benzene, naphthalene, indan, indene or the like, in which preferable one is benzene.

10 Preferred compound [I] is one having aryl or ar(lower)alkyl for R¹, aryl or ar(lower)alkyl for R², aryl or arylamino, each of which may be substituted with halogen for R³, CH or N for X, a single bond or -NH- for Y, and $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$ for Q; or one having lower alkenylene which may be substituted with aryl or may be condensed with benzene optionally substituted with lower alkoxy for R¹ and R² to be
15 taken together to form, aryl or arylamino, each of which may be substituted with halogen, pyridyl, or pyridylamino for R³, CH or N for X, a single bond or -NH- for Y, and $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$ for Q.

20 Suitable salts of the object compound [I] are pharmaceutically acceptable conventional non-toxic salts and include acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], a salt with an
25 amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.], a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.] and the like.

30 The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The compound [Ia] or its salt can be prepared by

reacting a compound [II] or its salt with a compound [III] or its reactive derivative at the carboxy group or a salt thereof.

5 Suitable salts of the compounds [Ia] and [II] may be the same as those exemplified for the compound [I].

 Suitable salts of the compound [III] and its reactive derivative at the carboxy group may be metal salt or alkaline earth metal salt as exemplified for the compound [I].

10 Suitable reactive derivative at the carboxy group or the compound [III] may include an ester, an acid halide, an acid anhydride and the like. The suitable examples of the reactive derivatives may be an acid halide [e.g. acid chloride, acid bromide, etc.];

 a symmetrical acid anhydride; a mixed acid anhydride with an acid such as aliphatic carboxylic acid [e.g. acetic acid, pivalic acid, etc.], substituted phosphoric acid [e.g. dialkylphosphoric acid, diphenylphosphoric acid, etc.]; an ester such as substituted or unsubstituted lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, hexyl ester, trichloromethyl ester, etc.], substituted or 20 unsubstituted ar(lower)alkyl ester [e.g. benzyl ester, benzhydryl ester, p-chlorobenzyl ester, etc.], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, 25 pentachlorophenyl ester, naphthyl ester, etc.], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole, 1-hydroxy-6-chloro-1H-benzotriazole, or the like. These reactive derivatives can be optionally selected according to the kind 30 of the compound [III] to be used.

 The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene dichloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other 35 organic solvent which does not adversely influence the

reaction. Among these solvents, hydrophilic solvent may be used in a mixture with water.

The reaction is also preferably carried out in the presence of a conventional base such as triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaminopyridine, etc., or a mixture thereof.

When the compound [III] is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, thionyl chloride, oxalyl chloride, lower alkoxycarbonyl halide [e.g. ethyl chloroformate, isobutyl chloroformate, etc.], 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

20 Process 2

The compound [Ib] or its salt can be prepared by reacting a compound [II] or its salt with a compound [IV].

Suitable salts of the compounds [Ib] and [II] may be the same as those exemplified for the compound [I].

25 This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, chloroform, methylene chloride or any other organic solvent which does not adversely influence the reaction.

30 The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 3

35 The compound [Ic] or its salt can be prepared by reacting a compound [V] or its salt with a compound [III] or its reactive derivative at the carboxy group or a salt

thereof.

Suitable salts of the compounds [Ic] and [V] may be the same as those exemplified for the compound [I].

5 Suitable salts of the compound [III] and its reactive derivative at the carboxy group may be metal salt or alkaline earth metal salt as exemplified for the compound [I].

10 This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 4

15 The compound [Id] or its salt can be prepared by reacting a compound [V] or its salt with a compound [IV].

Suitable salts of the compounds [Id] and [V] may be the same as those exemplified for the compound [I].

20 This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 2.

Process 5

25 The compound [Ie] or its salt can be prepared by reacting a compound [VI] or its reactive derivative at the carboxy group, or a salt thereof with a compound [VII] or its salt.

30 Suitable salts of the compounds [Ie], [VI] and its reactive derivative at the carboxy may be the same as those exemplified for the compound [I].

Suitable salt of the compound [VII] may be acid addition salt as exemplified for the compound [I].

35 This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and

reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

5 The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

10 It is to be noted that the compound [I] and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) or geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixture thereof are included within the scope of this invention.

15 Additionally, it is to be noted that any solvate [e.g. enclosure compound (e.g. hydrate, ethanolate, etc.)] of the compound [I] or a salt thereof is also included within the scope of this invention.

20 The object compound [I] and salts thereof possess strong potentiation of the cholinergic activity, and are useful for the treatment and/or prevention of disorders in the central nervous system for mammals, and more particularly of amnesia, dementia (e.g. senile dementia, Alzheimer's dementia, dementia associated with various diseases such as cerebral vascular dementia, cerebral post-traumatic dementia, dementia due to brain tumor, dementia due to chronic subdural

25 hematoma, dementia due to normal pressure hydrocephalus, post-meningitis dementia, Parkinson's disease type dementia, etc.) and the like. Additionally, the object compound is expected to be useful as therapeutical and/or preventive

30 agents for schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

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In order to illustrate the usefulness of the object compound [I], the pharmacological data of the compound [I] is shown in the following.

5 Test

Penile erection in rat

(This test was carried out according to a similar manner to that described in Jpn. J. Pharmacol., Vol. 64, 147-153 (1994))

10

(i) Method

Male Fischer 344 rats at the age of 8 weeks (n=7) were used. All rats were handled 3 minutes a day for three successive days before the tests. The rats were tested in groups of seven and various doses of the test compound were given in semi-randomized order. The test compounds were suspended in 0.5% methyl-cellulose immediately before use, and given intraperitoneally in a volume of 1 ml/kg just before the start of test. Immediately after injection, each rat was placed in a perspex box (25x25x35 cm) and its behavior was observed for 60 minutes, during which time the number of penile erections was counted. A mirror was situated behind each box to facilitate of the rat. Data was expressed as a mean number.

25

(ii) Test Result

Test Compound (Example No.)	Dose (mg/kg)	Penile Erection (Number/hr)
2	0.32	0.57
6	0.32	0.60
8	0.1	0.60
7	0.1	0.71

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It is clear that the compound having the above-mentioned activity ameliorates the memory deficits (i.e. amnesia,

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dementia, etc.) from the description in the Journal of Pharmacology and Experimental Therapeutics, Vo. 279, No. 3, 1157-1173 (1996). Further, it is expected that the compound having the above-mentioned activity is useful as
5 therapeutic and/or preventive agent for aforesaid diseases from some patent applications (e.g. PCT International Publication No. WO 98/27930, etc.).

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present
10 invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid, semi-solid or liquid excipient suitable for oral or parenteral administration. The
15 pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly
20 used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for
25 treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for
30 the purpose of illustrating this invention.

Preparation 1

To a solution of 4-methylcyclohex-3-enecarbonyl chloride (2 ml) in a mixture of methanol (20 ml) and tetrahydrofuran
35 (20 ml) was added aqueous sodium hydroxide (4N, 20 ml). The

resultant mixture was stirred at ambient temperature for 1 hour, and evaporated. The residue was taken up into a mixture of water and ethyl acetate and adjusted pH to around 1. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give 4-methylcyclohex-3-enecarboxylic acid, which was used without further purification.

NMR (DMSO- d_6 , δ) : 1.60 (3H, s), 1.35-1.65 (1H, m),
1.75-2.2 (5H, m), 2.25-2.45 (1H, m), 5.25-5.4 (1H,
m), 12.09 (1H, br s)

MASS (LD) (m/z) : 139.2

Preparation 2

To a solution of 4-methylcyclohex-3-enecarboxylic acid (1.7 g) and triethylamine (1.8 ml) in tert-butanol (35 ml) was added diphenylphosphoryl azide (2.6 ml), and the mixture was refluxed for 8 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate, washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was chromatographed on silica gel (150 ml) eluting with 1-3% ethyl acetate in n-hexane to give 1-tert-butoxycarbonylamino-4-methylcyclohex-3-ene (0.82 g).

NMR (DMSO- d_6 , δ) : 1.37 (9H, s), 1.60 (3H, s), 1.65-2.2 (6H, m), 3.2-3.4 (1H, m), 5.2-5.3 (1H, m), 6.68 (1H, br s)

MASS (LD) (m/z) : 234.3

Preparation 3

To a solution of 1-tert-butoxycarbonylamino-4-methylcyclohex-3-ene (0.4 g) in a mixture of anisole (0.4 ml) and dichloromethane (0.8 ml) was added trifluoroacetic acid (1.2 ml) at 0°C and the mixture was allowed to stir at 0°C for 1 hour. Evaporation gave a residue, which was taken up

into a solution of hydrogen chloride in dioxane (4N, 2 ml). Evaporation under reduced pressure and trituration with diisopropyl ether gave 1-amino-4-methylcyclohex-3-ene hydrochloride, which was used without further purification.

5

Example 1

A solution of 1,2,3,6-tetrahydropyridine (0.25 g) and 4-phenoxy-carbonylaminopyridine (0.64 g) in 1,2-dichloroethane (5 ml) was heated to 75°C for 6 hours. Evaporation of the solvent gave a residue, which was chromatographed on silica gel (50 ml) eluting with 0-5% methanol in dichloromethane, and taken up into a solution of hydrogen chloride in ethyl acetate (4N, 2 ml). Evaporation under reduced pressure and trituration with diisopropyl ether gave 1-(pyridin-4-ylcarbonyl)-1,2,3,6-tetrahydropyridine hydrochloride (0.43 g).

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NMR (DMSO-d₆, δ) : 2.05-2.35 (2H, m), 3.64 (2H, t, J=6Hz), 4.05 (2H, t, J=2.5Hz), 5.6-5.8 (1H, m), 5.8-6.0 (1H, m), 8.06 (2H, d, J=7Hz), 8.55 (2H, d, J=7Hz), 10.58 (1H, s), 14.72 (1H, br s)

MASS (LD) (m/z) : 204.2

Example 2

To a stirred solution of 1,2,3,6-tetrahydropyridine (82 mg) in tetrahydrofuran (2 ml) was added 4-fluorophenyl-isocyanate (0.112 ml) at ambient temperature. After stirring at ambient temperature for 10 hours, the solvent was removed by evaporation under reduced pressure, and the residue was triturated with diisopropyl ether to give 1-(4-fluorophenylcarbonyl)-1,2,3,6-tetrahydropyridine (117 mg).

30

NMR (DMSO-d₆, δ) : 2.0-2.2 (2H, m), 3.51 (2H, t, J=5.7Hz), 3.85-3.95 (2H, m), 5.65-5.95 (2H, m), 6.95-7.15 (2H, m), 7.35-7.55 (2H, m), 8.47 (1H, s)

MASS (LD) (m/z) : 243.1

35

Example 3

The following compound was obtained according to a similar manner to that of Example 2.

5 2-(4-Fluorophenylcarbamoyl)-1,2,3,4-tetrahydro-
isoquinoline

NMR (DMSO-d₆, δ) : 2.85 (2H, t, J=6Hz), 3.69 (2H, t, J=6Hz), 4.63 (2H, s), 7.07 (2H, t, J=9Hz), 7.18 (4H, s), 7.48 (2H, dd, J=5, 9Hz), 8.60 (1H, s)

10 MASS (LD) (m/z) : 293.2

Example 4

To a solution of 1-tert-butoxycarbonylamino-4-methylcyclohex-3-ene (0.18 g) in a mixture of anisole (0.18 ml) and dichloromethane (0.36 ml) was added trifluoroacetic acid (0.54 ml) at 0°C and the mixture was allowed to stir at 0°C for 1 hour. Evaporation gave a residue, which was taken up into 1,2-dichloroethane (5 ml). To the mixture were added triethylamine (0.6 ml) and 4-phenoxy-carbonylamino-pyridine (0.183 g), and the resultant mixture was heated to 75°C for 6 hours. Evaporation gave a residue, which was chromatographed on silica gel (50 ml) eluting with 7% methanol in dichloromethane, and taken up into a solution of hydrogen chloride in ethyl acetate (4N, 2 ml). Evaporation under reduced pressure and trituration with diisopropyl ether gave N-(4-methylcyclohex-3-en-1-yl)-N'-(pyridin-4-yl)urea hydrochloride (0.144 g).

NMR (DMSO-d₆, δ) : 1.64 (3H, s), 1.4-2.4 (6H, m), 3.6-3.9 (1H, m), 5.2-5.35 (1H, m), 7.26 (1H, d, J=8Hz), 7.82 (2H, d, J=7Hz), 8.51 (2H, d, J=7Hz), 10.91 (1H, s), 14.50 (1H, br s)

MASS (LD) (m/z) : 232.2

Example 5

35 To a suspension of 1-amino-4-methylcyclohex-3-ene

hydrochloride (0.103 g) in dichloromethane (5 ml) were added
in turn pyridine (0.14 ml) and 4-fluorobenzoyl chloride (83
μl) at 0°C. The mixture was allowed to warm to ambient
temperature and stirred for 1 hour, which was taken up into a
5 mixture of water and ethyl acetate. The separated organic
layer was washed in turn with hydrochloric acid (1N), aqueous
sodium hydrogen carbonate, and brine, and dried over
magnesium sulfate. Evaporation under reduced pressure gave a
residue, which was chromatographed on silica gel (50 ml)
10 eluting with 0-20% ethyl acetate in n-hexane to give 1-(4-
fluorobenzoylamino)-4-methylcyclohex-3-ene (98 mg).

NMR (DMSO-d₆, δ) : 1.59 (3H, s), 1.4-2.3 (6H, m), 3.8-
4.1 (1H, m), 5.35-5.5 (1H, m), 7.27 (2H, t, J=9Hz),
7.89 (2H, dd, J=5, 9Hz), 8.25 (1H, d, J=7Hz)

15 MASS (APCI) (m/z) : 234

Example 6

The following compound was obtained according to a
similar manner to that of Example 5.

20 2-(4-Fluorobenzoylamino)-1,2,3,4-tetrahydronaphthalene
NMR (DMSO-d₆, δ) : 1.65-1.9 (1H, m), 1.95-2.25 (1H, m),
2.7-3.1 (4H, m), 4.05-4.3 (1H, m), 7.08 (4H, s),
7.2-7.4 (2H, m), 7.85-8.05 (2H, m), 8.45 (1H, d,
25 J=7.5Hz)
MASS (APCI) (m/z) : 270

Example 7

To a suspension of 1-amino-4-methylcyclohex-3-ene
30 hydrochloride (103 mg) in dichloromethane (5 ml) were added
in turn pyridine (0.14 ml), 4-pyridinecarbonyl chloride
hydrochloride (0.124 g) and N,N-dimethylaminopyridine (0.11 g)
at 0°C. The mixture was allowed to warm to ambient
temperature and was allowed to stir for 1 hour. The reaction
35 mixture was taken up into a mixture of water and ethyl

acetate, and adjusted pH to 4.6. The separated organic layer was washed in turn with water and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give
5 1-(pyridin-4-ylcarbonylamino)-4-methylcyclohex-3-ene (46 mg).

NMR (DMSO- d_6 , δ) : 1.64 (3H, s), 1.45-3.35 (6H, m),
3.8-4.1 (1H, m), 5.25-5.45 (1H, m), 7.74 (2H, dd,
J=1.6, 4.5Hz), 8.53 (1H, d, J=7.5Hz), 8.70 (2H, dd,
J=1.6, 4.5Hz)

10 MASS (APCI) (m/z) : 217

Example 8

The following compound was obtained according to a similar manner to that of Example 7.

15

2-(Pyridin-4-ylcarbonylamino)-1,2,3,4-tetrahydro-naphthalene

NMR (DMSO- d_6 , δ) : 1.65-1.9 (1H, m), 1.95-2.15 (1H, m),
2.7-3.15 (4H, m), 4.05-4.3 (1H, m), 7.10 (4H, s),
20 7.78 (2H, dd, J=1.6, 4.5Hz), 8.65-8.8 (3H, m)

MASS (APCI) (m/z) : 253

Example 9

1) To a solution of 1-tert-butoxycarbonylamino-4-methylcyclohex-3-ene (0.18 g) in a mixture of anisole (0.18 ml) and dichloromethane (0.36 ml) was added trifluoroacetic acid (0.54 ml) at 0°C and the mixture was allowed to stir at 0°C for 1 hour. Evaporation gave a residue containing 1-amino-4-methylcyclohex-3-ene.

30

2) The residue containing 1-amino-4-methylcyclohex-3-ene was taken up into dichloromethane (5 ml). To the mixture were added triethylamine (0.6 ml) and 4-fluorophenyl-isocyanate (97 μ l) at 0°C and the resultant mixture was
35 allowed to stir for 30 minutes at 0°C. Evaporation under

reduced pressure gave a residue, which was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed with brine, evaporated under reduced pressure, and triturated with n-hexane to give N-(4-methylcyclohex-3-en-1-yl)-N'-(4-fluorophenyl)urea (0.206 g).

NMR (DMSO-d₆, δ) : 1.63 (3H, s), 1.3-1.9 (3H, m), 1.9-2.1 (2H, m), 2.1-2.4 (1H, m), 3.6-3.85 (1H, m), 5.25-5.35 (1H, m), 6.07 (1H, d, J=8Hz), 7.04 (2H, t, J=9Hz), 7.36 (2H, dd, J=5, 9Hz), 8.38 (1H, s)

MASS (LD) (m/z) : 271.2

Example 10

The following compound was obtained by using 2-amino-1,2,3,4-tetrahydronaphthalene as a starting compound according to a similar manner to that of Example 2.

N-(4-Fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)urea

NMR (DMSO-d₆, δ) : 1.6-1.8 (1H, m), 1.8-2.05 (1H, m), 2.63 (1H, dd, J=8, 16Hz), 2.83 (2H, t, J=7Hz), 3.02 (1H, dd, J=5, 16Hz), 3.8-4.1 (1H, m), 6.22 (1H, d, J=7.5Hz), 6.95-7.2 (2H, m), 7.12 (4H, s), 7.3-7.45 (2H, m), 8.40 (1H, s)

MASS (APCI) (m/z) : 285

Example 11

To a solution of aminodiphenylmethane (0.4 g) in dichloromethane (5 ml) were added in turn pyridine (0.21 ml) and 4-fluorobenzoyl chloride (0.23 ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with

diisopropyl ether to give (4-fluorobenzoylamino)-
diphenylmethane (0.49 g).

NMR (DMSO- d_6 , δ): 6.40 (1H, d, J=9Hz), 7.2-7.45 (12H,
m), 8.01 (2H, dd, J=5, 9Hz), 9.30 (1H, d, J=9Hz)

5 MASS (APCI) (m/z): 306

Example 12

To a solution of 4-fluoroaniline (0.2 g) in
dichloromethane (10 ml) were added in turn pyridine (0.19 ml)
10 and diphenylcarbonyl chloride (0.417 g) at 0°C. The mixture
was allowed to warm to ambient temperature and stirred for 10
hours, and to the mixture was added N,N-dimethylaminopyridine
(0.22 g), and the mixture was allowed to stir for another 1
hour. The reaction mixture was taken up into a mixture of
15 water and ethyl acetate. The separated organic layer was
washed in turn with hydrochloric acid (1N), aqueous sodium
hydrogen carbonate and brine, and dried over magnesium
sulfate. Evaporation under reduced pressure gave a residue,
which was triturated with diisopropyl ether to give N,N-
20 diphenyl-N'-4-fluorophenylurea (0.384 g).

NMR (DMSO- d_6 , δ): 7.07 (2H, t, J=9Hz), 7.15-7.3 (6H, m),
7.3-7.5 (6H, m), 8.45 (1H, s)

MASS (APCI) (m/z): 307

25 Example 13

To a solution of (R)-1,2,3,4-tetrahydronaphthalen-2-
ylamine hydrochloride (0.9 g) in dichloromethane (15 ml) were
added in turn triethylamine (1.71 ml) and 4-fluorobenzoyl
chloride (0.58 ml) at 0°C. The mixture was allowed to warm
30 to ambient temperature and stirred for 1 hour, which was
taken up into a mixture of water and ethyl acetate. The
separated organic layer was washed in turn with hydrochloric
acid (1N), aqueous sodium hydrogen carbonate and brine, and
dried over magnesium sulfate. Evaporation under reduced
35 pressure gave a residue, which was triturated with

diisopropyl ether to give (R)-4-fluoro-N-(1,2,3,4-tetrahydronaphthalen-2-yl)benzamide (1.26 g).

NMR (DMSO- d_6 , δ): 1.60-1.89 (1H, m), 1.95-2.16 (1H, m),
2.70-3.14 (4H, m), 4.05-4.30 (1H, m), 7.09 (4H, s),
7.30 (2H, t, $J=8.9\text{Hz}$), 7.86-8.04 (2H, m), 8.45 (1H,
d, $J=7.6\text{Hz}$)

MASS (APCI) (m/z): 270.3

Example 14

To a solution of (S)-1,2,3,4-tetrahydronaphthalen-2-ylamine hydrochloride (0.9 g) in dichloromethane (15 ml) were added in turn triethylamine (1.71 ml) and 4-fluorobenzoyl chloride (0.58 ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give (S)-4-fluoro-N-(1,2,3,4-tetrahydronaphthalen-2-yl)benzamide (1.26 g).

NMR (DMSO- d_6 , δ): 1.60-1.89 (1H, m), 1.95-2.16 (1H, m),
2.70-3.14 (4H, m), 4.05-4.30 (1H, m), 7.09 (4H, s),
7.30 (2H, t, $J=8.9\text{Hz}$), 7.86-8.04 (2H, m), 8.45 (1H,
d, $J=7.6\text{Hz}$)

MASS (APCI) (m/z): 270.3

Example 15

To a solution of 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamine (0.49 g) in dichloromethane (5 ml) were added in turn pyridine (0.29 ml) and 4-fluorobenzoyl chloride (0.33 ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous

sodium hydrogen carbonate and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-fluoro-N-(7-methoxy-1,2,3,4-tetrahydronaphthalene-2-yl)-

5 benzamide (497 mg).

NMR (DMSO-d₆, δ): 1.60-1.85 (1H, m), 1.92-2.13 (1H, m),
2.63-3.10 (4H, m), 3.70 (3H, s), 4.00-4.25 (1H, m),
6.60-6.79 (2H, m), 7.00 (1H, d, J=8.2Hz), 7.30 (2H,
10 t, J=8.9Hz), 7.89-8.04 (2H, m), 8.44 (1H, d,
J=7.6Hz)

MASS (APCI) (m/z): 300

Example 16

To a solution of 6-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamine (0.57 g) in dichloromethane (5 ml) were added in
15 turn triethylamine (0.46 ml) and 4-fluorobenzoyl chloride (0.30 ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated organic
20 layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-fluoro-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-
25 benzamide (0.59 g).

NMR (DMSO-d₆, δ): 1.60-1.85 (1H, m), 1.92-2.10 (1H, m),
2.60-3.07 (4H, m), 3.71 (3H, s), 4.00-4.30 (1H, m),
6.60-6.75 (2H, m), 6.99 (1H, d, J=8.2Hz), 7.30 (2H,
30 t, J=8.9Hz), 7.80-8.04 (2H, m), 8.42 (1H, d,
J=7.6Hz)

MASS (APCI) (m/z): 300

Example 17

To a solution of indan-2-ylamine (0.297 g) in
35 dichloromethane (5 ml) were added in turn pyridine (0.23 ml)

and 4-fluorobenzoyl chloride (0.26 ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-fluoro-N-(indan-2-yl)benzamide (0.325 g).

10 NMR (DMSO-d₆, δ): 2.94 (2H, dd, J=6.7, 16.0Hz), 3.24 (2H, dd, J=6.7, 16.0Hz), 4.55-4.80 (1H, m), 7.06-7.40 (6H, m), 7.83-8.04 (2H, m), 8.67 (1H, d, J=6.7Hz)

15 MASS (APCI) (m/z): 256

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CLAIMS

1. A compound of the formula:



wherein R^1 and R^2 are each aryl or ar(lower)alkyl, or
are taken together to form lower alkylene
or lower alkenylene, each of which may be
substituted with aryl or may be condensed
with a cyclic hydrocarbon optionally
substituted with lower alkyl, lower
alkoxy, aryl, aryloxy or halogen,

R^3 is lower alkyl, lower alkoxy, aryl, arylamino
or aryloxy, each of which may be
substituted with lower alkoxy or halogen,
pyridyl, or pyridylamino,

X is CH or N,

Y is a single bond or -NH-, and

Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$,

provided that

1) when R^3 is arylamino which may be substituted with
lower alkoxy or halogen, or pyridylamino,

then X is CH or

Y is a single bond,

2) when R^1 and R^2 are taken together to form pentenylene
condensed with benzene optionally substituted
with lower alkyl, lower alkoxy, aryl or
halogen,

X is CH,

Y is -NH-, and

Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$,

then R^3 is phenyl substituted with halogen,
phenylamino substituted with halogen, or
pyridyl, or

3) when R^1 and R^2 are taken together to form butenylene
condensed with benzene,

X is CH,

Y is -NH-, and

Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$,

then R^3 is phenyl substituted with halogen, and the
indan ring to form by taking together

R^1 , R^2 and X is substituted by -Y-Q- R^3 at the
2-position,

and its salt.

2. A compound according to claim 1, wherein

R^1 and R^2 are taken together to form lower alkenylene
which may be substituted with aryl or may be
condensed with benzene optionally substituted with
lower alkoxy,

R^3 is aryl or arylamino, each of which may be
substituted with halogen, pyridyl, or pyridylamino.

3. A compound according to claim 2, wherein

X is N.

4. A compound according to claim 2, wherein

X is CH, and

Y is -NH-.

5. A compound according to claim 3, wherein

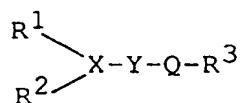
R^1 and R^2 are taken together to form methylpentenylene
or pentenylene which may be condensed with benzene,
and

R^3 is arylamino which may be substituted with halogen,

or pyridylamino.

6. A compound according to claim 4, wherein
 R^1 and R^2 are taken together to form methylpentenylenes,
 5 butenylenes condensed with benzene, or pentenylenes which
 may be condensed with benzene optionally substituted
 with lower alkoxy.

7. A compound of the formula:



wherein R^1 and R^2 are each aryl or ar(lower)alkyl, or
 15 are taken together to form lower alkylene
 or lower alkenylene, each of which may be
 substituted with aryl or may be condensed
 with a cyclic hydrocarbon optionally
 substituted with lower alkyl, lower
 20 alkoxy, aryl, aryloxy or halogen,
 R^3 is lower alkyl, lower alkoxy, aryl, arylamino
 or aryloxy, each of which may be
 substituted with lower alkoxy or halogen,
 pyridyl, or pyridylamino,

25 X is CH or N,

Y is a single bond or -NH-, and

Q is $\overset{\text{O}}{\parallel}\text{-C-}$,

provided that

- 30 1) when R^3 is arylamino which may be substituted with
 lower alkoxy or halogen, or pyridylamino,

then X is CH or

Y is a single bond,

- 2) when R^1 and R^2 are taken together to form pentenylenes
 35 condensed with benzene optionally substituted

with lower alkyl, lower alkoxy, aryl or
halogen,

X is CH,

Y is -NH-, and

5

Q is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$,

then R³ is phenyl substituted with halogen,

phenylamino substituted with halogen, or

pyridyl, or

10

3) when R¹ and R² are taken together to form butenylene
condensed with benzene,

X is CH,

Y is -NH-, and

15

Q is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$,

then R³ is phenyl substituted with halogen, and the

indan ring to form by taking together

R¹, R² and X is substituted by -Y-Q-R³ at the

2-position,

20

or its salt, which comprises,

1) reacting a compound of the formula:

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or its salt with a compound of the formula:

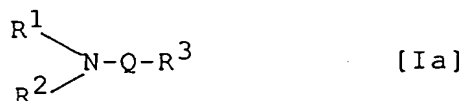
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or its reactive derivative at the carboxy group

or a salt thereof to provide a compound of the formula:

35



or its salt, in the above formulas,
R¹, R², R³ and Q are each as defined above, or

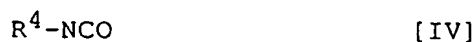
2) reacting a compound of the formula:

5



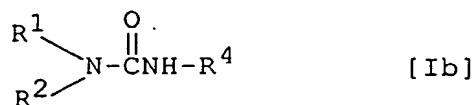
or its salt with a compound of the formula:

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to provide a compound of the formula:

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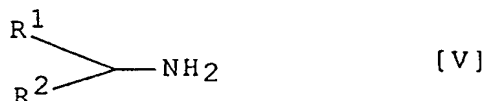


or its salt, in the above formulas,
R¹ and R² are each as defined above, and
R⁴ is aryl which may be substituted with lower alkoxy
or halogen, or pyridyl, or

20

3) reacting a compound of the formula:

25



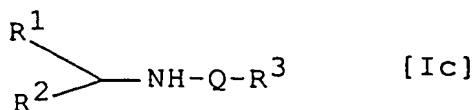
or its salt with a compound of the formula:

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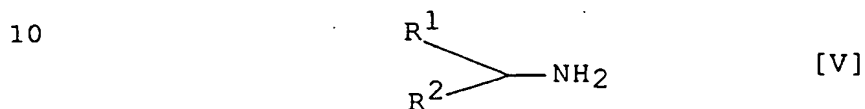
or its reactive derivative at the carboxy group
or a salt thereof to provide a compound of the formula:

35

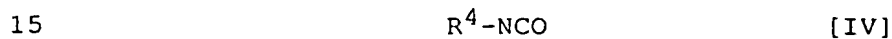


5 or its salt, in the above formulas,
 R^1 , R^2 , R^3 and Q are each as defined above, or

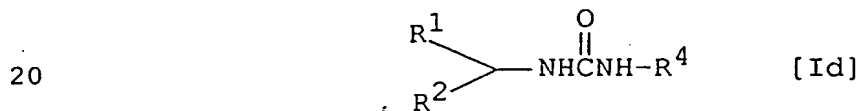
4) reacting a compound of the formula:



or its salt with a compound of the formula:

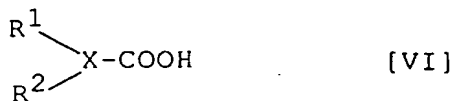


to provide a compound of the formula:



or its salt, in the above formulas,
 R^1 , R^2 and R^4 are each as defined above, or

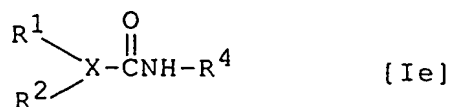
5) reacting a compound of the formula:



or its reactive derivative at the carboxy group or a
 salt thereof with a compound of the formula:



or its salt to provide a compound of the formula:



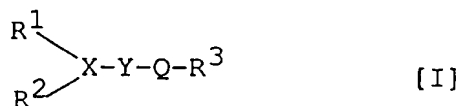
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or its salt, in the above formulas,
 R^1 , R^2 , R^4 and X are each as defined above.

10 8. A pharmaceutical composition comprising a compound of
 claim 1, as an active ingredient, in association with a
 pharmaceutically acceptable, substantially non-toxic
 carrier or excipient.

15 9. A compound of claim 1 for use as a medicament.

20 10. A method for therapeutic treatment and/or prevention of
 amnesia or dementia which comprises administering an
 effective amount of a compound of the following formula
 to mammals.



25 wherein R^1 and R^2 are each aryl or ar(lower)alkyl, or
 are taken together to form lower alkylene
 or lower alkenylene, each of which may be
 substituted with aryl or may be condensed
 with a cyclic hydrocarbon optionally
 30 substituted with lower alkyl, lower
 alkoxy, aryl, aryloxy or halogen,
 R^3 is lower alkyl, lower alkoxy, aryl, arylamino
 or aryloxy, each of which may be
 substituted with lower alkoxy or halogen,
 35 pyridyl, or pyridylamino,

X is CH or N,

Y is a single bond or -NH-, and

Q is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$,

5 or its salt.

11. Use of the compound as defined in claim 10 for
manufacture of a medicament for treating and/or
preventing amnesia or dementia in mammals.

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INTERNATIONAL SEARCH REPORT

Index and Application No

PCT/JP 00/00601

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C233/65 C07C275/30 C07D211/68 C07D217/06 C07D213/56
 A61K31/44 A61K31/16 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 8 287 M (DELALANDE SA) 9 November 1970 (1970-11-09) table 2	1,7-9
X	EP 0 306 375 A (SYNTHELABO) 8 March 1989 (1989-03-08) example 1	1,2,4,6, 7
X	YEUNG, J.M. & KNAUS, E.E.: "Synthesis of 3,6-dihydro-1(2H)-pyridinyl derivatives with hyperglycemic activity" EUR. J. MED. CHEM. - CHIM- THER, vol. 21, no. 3, 1986, pages 181-185, XP000882437 example 9C	1,2,4, 6-9
	--- -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 May 2000

Date of mailing of the international search report

22.05.00

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Janus, S

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/JP 00/00601

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AGWADA, V.: "Potential Central Nervous System Active Agents. 3. Synthesis of Some Substituted Benzamides and Phenylacetamides" J. CHEM. ENG. DATA, vol. 29, no. 2, 1984, pages 231-235, XP000882455 example VID ----	1,7-9
Y	US 4 797 419 A (MOOS WALTER H ET AL) 10 January 1989 (1989-01-10) tables 1-3 ----	1-11
Y	EP 0 343 961 A (AMERICAN HOME PROD) 29 November 1989 (1989-11-29) the whole document ----	1-11
Y	PATENT ABSTRACTS OF JAPAN vol. 018, no. 385 (C-1227), 20 July 1994 (1994-07-20) & JP 06 107544 A (TAISHO PHARMACEUT CO LTD), 19 April 1994 (1994-04-19) abstract ----	1-11
Y	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 01, 28 February 1995 (1995-02-28) & JP 06 298732 A (TAISHO PHARMACEUT CO LTD), 25 October 1994 (1994-10-25) abstract -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 00/00601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 7
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

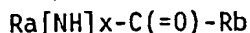
International Application No. PCT/JP 00/00601

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7

The present compound claims relate to an extremely large number of possible compounds. For instance, a well-known compound such as N,N-diphenylacetamide falls within the scope of claim 1. Support within the meaning of Article 6 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the following formula, drawn in the light of the actual compounds prepared in the examples :



wherein

Ra is either a 4-fluorophenyl or a pyridin-4-yl group,

x is 0 or 1

Rb is a diphenylmethylamino group, an indan-2-ylamino group, a 1,2,3,4-tetrahydronaphthalenylamino group possibly substituted on either the 6- or 7- position by a methoxy group, a 4-methylcyclohex-3-en-1-ylamino group, a 1,2,3,6-tetrahydropyridin-1-yl group or a 1,2,3,4-tetrahydroisoquinolin-2-yl group.

In addition, claim 7 has not been searched, since it is drafted as a compound claim, but includes essentially only process features; it is therefore impossible to determine whether the claims relates to a process or to compounds, reason for which its subject-matter is so unclear that no search could possibly be performed.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/JP 00/00601

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
FR 8287	M	09-11-1970	FR 1604469 A	08-11-1971
EP 0306375	A	08-03-1989	FR 2619110 A	10-02-1989
			FR 2625504 A	07-07-1989
			FR 2630113 A	20-10-1989
			FR 2630114 A	20-10-1989
			AU 598149 B	14-06-1990
			AU 2047588 A	09-02-1989
			CZ 9104051 A	17-02-1993
			DK 437588 A	28-03-1989
			FI 883667 A	08-02-1989
			FR 2634204 A	19-01-1990
			FR 2634205 A	19-01-1990
			HU 47562 A	28-03-1989
			JP 1100167 A	18-04-1989
			NO 883485 A	08-02-1989
			NZ 225708 A	26-04-1990
			PT 88204 A	30-06-1989
			US 4885302 A	05-12-1989
			US 4945096 A	31-07-1990
			ZA 8805786 A	26-04-1989
US 4797419	A	10-01-1989	NONE	
EP 0343961	A	29-11-1989	AT 132862 T	15-01-1996
			AU 628341 B	17-09-1992
			AU 3502589 A	30-11-1989
			CA 1340113 A	03-11-1998
			DE 68925385 D	22-02-1996
			DE 68925385 T	15-05-1996
			DK 249989 A	25-11-1989
			ES 2081302 T	01-03-1996
			FI 892424 A,B,	25-11-1989
			GB 2218988 A,B	29-11-1989
			GR 3019217 T	30-06-1996
			HU 53095 A,B	28-09-1990
			IE 64151 B	12-07-1995
			IL 90279 A	30-03-1995
			JP 2015059 A	18-01-1990
			JP 2711284 B	10-02-1998
			KR 128345 B	03-04-1998
			NZ 229225 A	21-12-1990
			PT 90633 A,B	30-11-1989
			US 5482940 A	09-01-1996
			US 5380725 A	10-01-1995
			US 5010078 A	23-04-1991
			US 5106849 A	21-04-1992
			US 5278160 A	11-01-1994
			US 5254552 A	19-10-1993
			ZA 8903836 A	30-01-1991
JP 06107544	A	19-04-1994	NONE	
JP 06298732	A	25-10-1994	NONE	